REMARKS

Amendments to the Specification

Applicants have amended page 32 of the specification to improve its form and delete references to embedded hyperlinks, in accordance with the Examiner's suggestion. This amendment brings the specification in compliance with MPEP §608.01.

The Claim Amendments

Applicants have amended claims 1, 4, 6, 8 and 36 and have canceled claims 2 and 3. These claim amendments and cancellations are made expressly without waiver of applicants' rights to file for and to obtain claims directed to the cancelled or amended subject matter in this application or subsequent applications claiming benefit herefrom.

Applicants have amended claim 1 to recite an isolated polynucleotide encoding a human hPXR polypeptide or fragment thereof, wherein the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 112. These amendments improve the form of the claim and are supported throughout the specification, e.g., page 1, first full paragraph; page 16, lines 2-6; and page 35, Example 2.

Applicants have amended claims 4, 6, and 8 and 36 to improve their form and correct improper multiple dependencies, as requested by the Examiner.

None of the amendments to the claims constitutes new matter. Their entry is requested. Upon entry of these amendments, claims 1, 4-8, 34, 36 and 37 are now pending in this application.

The Rejections

35 U.S.C. §112, First Paragraph – Written Description

The Examiner has rejected claim 2 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the claim is drawn to a polynucleotide that encodes a variant hPXR protein or fragment thereof, without reciting any particular biological activity or other distinguishing feature. The Examiner therefore contends that the claim is drawn to a genus of nucleic acids that is defined solely by sequence identity and there is not sufficient written description of the claimed genus. The Examiner contends that the activation of a variant hPXR by rifampicin is not specific because the specification does not disclose any specific effect on variants. Applicants traverse.

The invention is based on applicants' discovery of phenotypic change associated with an amino acid substitution that results from a nucleotide change in a variant of the hPXR gene. The hPXR gene binds to a response element in the CYP3A4 promoter as a heterodimer and serves as a key transcriptional regulator of the cytochrome P450 3A4 (CYP3A4) gene. See, page 5, paragraph 2-3. Specifically, applicants discovered that a variant hPXR

polypeptide (D163G) containing a change from aspartic acid (D) to glycine (G) at residue 163 resulting from a polymorphism at position 488 of the hPXR gene (Accession No.: gi3769583, wherein the C of the CTG translation initiation site at position 280 has been numbered +1) (See, e.g., page 42, Table 4; and page 93, claim 1 as originally filed) results in impaired transcriptional activity compared to the wild type hPXR protein. A portion of the hPXR nucleotide sequence containing this polymorphism is provided in SEQ ID NO: 112.

Accordingly, amended claim 1 is drawn to an isolated polynucleotide encoding a variant hPXR polypeptide or fragment thereof wherein the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 112. Every member of the genus of polynucleotides encodes a variant hPXR polypeptide or a fragment of said polypeptide, and share a common structural element -- the nucleotide sequence of SEQ ID NO: 112 which includes the above-described nucleotide polymorphism. But applicants provide even more than this – they also demonstrate the function corresponding to this structural feature shared by all members of the claimed genus, i.e., the impaired transcriptional activity resulting from the D to G change encoded by the nucleotide sequence in SEQ ID NO: 112.

More particularly, the instant application discloses, on pages 36-37, Example 4, the functional consequences of specific genetic variants of hPXR. The application teaches that the variant hPXR polypeptide or fragment containing the D to G change at residue 163 has an impaired transcriptional activity upon treatment with rifampicin compared to a wild type hPXR

protein. *See, e.g.,* Figure 6A, which reveals that treatment with rifampicin decreased transcription of the reporter gene by 50% in the D163G variant as compared to wild type activity. The D163G variant also showed a strongly reduced basal activity, independent of treatment, at approximately 10% of the wild type activity. *See*, e.g., page 37, lines 10-12 and Figure 6B. The D163G variant corresponds an hPXR variant having the nucleic acid sequence of SEQ ID NO: 112. *See, e.g.,* page 42, Table 5, the second variant in exon 4, wherein the mutated sequence is SEQ ID NO:112. *See also*, page 42, Table 4, wherein the predicted effect of the hPXR variant M11 corresponds to that of D163G, i.e., SEQ ID NO:112.

Applicants submit that the specification describes the specific functional effects of the claimed variant on activity -- both in the basal state and upon activation by rifampicin. The activation of the claimed polynucleotide is specific. Applicants have obviated the Examiner's objection by amending claim 1 to recites a polynucleotide characterized by both sequence identity and biological activity. The instant application teaches this structure function relationship and thus fulfills the written description requirement. Applicants therefore request that the Examiner reconsider and withdraw this objection.

35 U.S.C. §102(b) – Anticipation

Hwang

The Examiner has rejected claims 1-2 under 35 U.S.C. §102(b) as being anticipated by Hwang et al., Genomics 30:293298, 1995: Accession R57588, GI: 827441 ("Hwang"). The Examiner states that Hwang teaches a polynucleotide sequence GI:827441 that is 100% identical to the polynucleotide sequence of SEQ ID NO:112. Applicants traverse, in view of the claim amendments.

Amended claim 1 recites a polynucleotide encoding a variant hPXR protein or fragment thereof wherein the polynucleotide has the nucleic acid sequence of SEQ ID NO: 112 and wherein the variant hPXR protein or fragment has an impaired transcriptional activity upon treatment with rifampicin compared to a wild type hPXR protein. The alleged sequence* in Hwang does not correspond to a polynucleotide encoding a variant hPXR protein or fragment with an impaired transcriptional activity upon treatment with rifampicin compared to a wild type hPXR protein of the claims. The Hwang sequence is not within an hPXR-encoding sequence. It does not anticipate the subject matter of the amended claims. Applicants therefore request that the Examiner reconsider and withdraw this objection.

Mittman

* The Examiner refers to appendix A for the sequence alignment. Applicants note that they did not receive an appendix A with a sequence alignment accompanying the Office Action. However, applicants have located a sequence in Hwang, having Accession No. F57383, that aligns with SEQ ID NO:112 as part of its reverse complement strand.

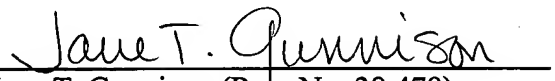
The Examiner has rejected claims 1-2 under 35 U.S.C. §102(b) as being anticipated by Mittman et al., U.S. Patent 6,821,724 ("Mittman"). The Examiner states that the polynucleotide sequence of SEQ ID NO:49096 from nucleotide 9-19 disclosed in Mittman is identical to the sequence of SEQ ID NO:112. The Examiner further states that Mittman teaches the use of nucleic acid for medical diagnosis. Applicants traverse, in view of the claim amendments and the below remarks.

Mittman's SEQ ID NO:49096, nucleotides 9-19, are not identical to the sequence claimed in the present invention. Applicants note, however, that the SEQ ID NO:49096 in Mittman does not correspond to the polynucleotide of amended claim 1, encoding a variant hPXR protein or fragment thereof wherein the polynucleotide has the nucleic acid sequence of SEQ ID NO: 112. Applicants note that nucleotides 9-19 of SEQ ID NO:49096 are identical to the sequence of SEQ ID NO:112, disclosed herein. Nonetheless, the Mittman sequence is not within the hPXR gene. It does not anticipate the subject matter of the amended claims. Applicants therefore request that the Examiner reconsider and withdraw this objection.

Conclusion

Applicants request favorable consideration and early allowance of the elected claims.

Respectfully submitted,



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